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THE SEARCH FOR PRINCIPLES OF NEURONAL ORGANIZATION

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To say that the brain is complex is to state the obvious, and yet from that statement inevitably comes the realization that there will be no single explanation of how it works. Our understanding is likely to accumulate by the identification of general principles of organization at many levels. Recognizing the necessity for an interdisciplinary approach, this conference dealt with developmental, anatomical, physiological and biochemical levels of explanation. The deliberately intimate size of the conference prevented the inclusion of many exciting molecular neurobiological studies.

What forms of explanation or principles of neuronal action are being sought? Are they to be broad principles, akin to some of those in physics, or are they to be more specific? If broad then we can at present offer none; if specific then we can offer many: for example, the neurone, the synapse, the channel, the action potential, the synaptic potential, numerous ionic currents, chemical transmitters, neuromodulators, hormones, excitation, inhibition, graded voltage signals, spike coding etc. The fact that we do not regard these as satisfying principles, but simply as lists of components and their actions, merely serves to emphasize how widely accepted they now are. We tend to forget how recent many of these concepts are: the neurone concept is only 80 years old, the acceptance of chemical synapses in the brain 50 years old, whilst the discovery of various currents is still continuing. Perhaps too we see how easily these seemingly unifying concepts can be split still further, as T. H. Bullock is always reminding us. Instead of either broad or specific principles what we seem to need are intermediate levels of principles to satisfy our desire to see some simplicity in the immense complexity of the brain. The best analogy I can draw is with electronic circuits. Descriptions of these are now possible in terms of integrated circuits, operational amplifiers and sample and hold circuits instead of the individual components themselves. Computer manufacturers now conceive of building machines – or at least talk glibly about such projects – that would contain as many components and interactions as in the human brain, with the knowledge that they will know how they work because they have the means to describe and explain complexity of that magnitude.

The closest that neurobiologists can come to these intermediate levels of description are, for example, the organization of neurones on the sensory side to provide centre-surround analysis, or lateral inhibition. On the motor side there are virtually none of these types of organizational principles. Faced with an apparent lack of success in providing principles of this type, there has been growing pessimism within the ranks of many neurobiologists and growing dissatisfaction with their efforts from without. The question that is always posed is whether their efforts will produce anything more than a massive amount of facts that pertain only to the nervous system or even the small part of that nervous system under study.

At the outset it must be realized that the approach which is adopted will determine in large part the generality of any principle that is likely to emerge. A continuum of approaches can be recognized, at one extreme of which the results are likely to be generalized, but at the other end they will not. For example, work that concentrates on the action of a component may be generalized to wherever that component occurs. A particular current may have features that are very similar no matter where it occurs. Action potentials can only be generated by a limited number of mechanisms. As we progress to a consideration of the way that information is transferred from one neurone to the next we again see only a limited number of mechanisms, but here some of the long held generalities start to break down. Spikes are not the necessary signals in many neurones for the release of transmitter. Interactions may occur through mechanisms that are non-synaptic; extracellular potassium ions can evoke potentials that are difficult to distinguish from the more conventional synaptic potentials (see chapter by Spira). Soups of neuromodulators, perhaps released locally, may act on receptors not necessarily grouped at discrete points.

With studies of the function of neuronal ensembles, the obvious generalities become fewer: an ensemble is present for a particular function, or set of functions such as moving a particular appendage, or processing a particular feature of a stimulus. The problem becomes one of whether by studying how an insect sees (see chapter by Shaw), a crayfish performs a tail flip (Wine), or a lamprey or tadpole swims (Grillner and Roberts), we will be able to describe features that are applicable beyond the example in question. Far less confidence exists that these studies will reveal general principles than exists, for example, in the studies of the cellular basis of learning in molluscs (see chapters by Alkon and Hawkins). It is also tacitly assumed for the moment that the studies of the ways ensembles of neurones develop will produce general rules (see chapters by Bastiani and Levine). It seems illogical to me to have more doubts about the physiological results, but a prevalent disillusionment with this whole area does exist; many of the studies are now classed simply as 'aardvarkism' – the study of yet another animal in which the pattern of movement or the way it is controlled is just a little different. I strongly reject such pessimism about this vital range of studies.

As studies progress to behaviour, they gradually become more self-limiting. What is discovered may be very relevant for the behaviour being studied in that particular species, but may have no relevance to any other behaviour or any other species. In the best examples the results can be extrapolated to other behaviour in other animals: in the worst they cannot.

Whenever pessimism about the lack of generalities surfaces, it is always worth comparing what we know now with what was known as recently as 30 years ago. The comparison is salutory. Take the control of movement as an example. Even where little is known of the action of individual neurones, as in the control of locomotion in the cat, the descriptions that are available are satisfying at their own particular level; for example, in terms of which areas of the brain and spinal cord are responsible for initiating and then maintaining the rhythm, the movements of a leg during the step cycle, and the sensory influences on the timing of the stance and swing phases.

features in common with other pattern generators in other diverse animals can already be recognized. Where much is known about the actions of individual nerve cells, as in the stomatogastric ganglion of the lobster or the segmental ganglia of arthropods or the leech, the level of description now available is quite phenomenal.

Many neuroscientists seem to feel guilty about the level of the explanations they are proposing: those working on the physiology of neurones imagine that explanations in terms of molecules would be more satisfying. This stems in large part from the introduction of many new molecular biological methods that can now be applied to the brain. The introduction of any new method always leads to an initial expansive period when numerous new descriptions become possible. These themselves do not offer explanations, but the sheer volume of papers that they generate are viewed alongside those produced by existing methodologies whose descriptive phases are generally past and which are being used to grapple with difficult problems.

Do we already have principles that we simply fail to recognize? Three examples can serve to indicate that this may be so. First, afferents from external mechanoreceptors seem to make excitatory connections in the central nervous system, and do not connect directly with motor neurones. When stated in this way it is seen to be true in a large majority of examples (most hair afferents make excitatory connections with interneurones), but incorrect in a few (some afferents from hair plates in insects synapse directly upon motor neurones). Does the fact that this idea is wrong sometimes invalidate it as a principle? Probably not, for if a principle is to be correct all of the time, it may have to be so broad as to be relatively meaningless. Second, local interneurones are a way of reducing complexity of connections. The receptive field of a motor neurone may be large and for all the afferents to connect directly with all the required motor neurones would necessitate complex neuronal projections. The interpolation of local interneurones allows simpler afferent projections with less complex rules for growth and connectivity. The afferents can project according to their position in three dimensional space on the body and particular interneurones can sample from that field, and according to its distribution, project it to the relevant motor neurones (see chapters by Murphey and Siegler). Third, the problem of why there should be so many transmitters has been posed many times: why not use just two, one to excite, the other to inhibit? The answer is now seen to lie in the use to which the different effects of the various transmitters can be put (see chapters by Marder and Pitman). They may open or close channels, activate voltage or non-voltage dependent channels, bring about changes on the postsynaptic neurone akin to those effected by proctolin on skeletal muscle, or differ markedly in the time course of their effects. Bath application of different putative transmitters or neuromodulators to a stomatogastric ganglion can produce distinctive changes in its pattern of motor output. Perhaps economy demands that one circuit be built for a particular set of patterns. Local release can then modify the circuit and produce as many other patterns as there are transmitters or neuromodulators.

Much of the foregoing has attempted to point out the difficulties in defining what a principle of neuronal action might be, and to dispel the pessimism that has arisen because so few principles seem to have emerged from so much effort. The following chapters speak even more forcibly in favour of my contentions. They show clearly what immense vitality there is in modern neurobiology, and how the molecular techniques are being integrated with the older ones to make an infinitely stronger subject which is likely to provide even greater insights into the way that the brain is organized.

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